PATENT COOPERATION TREATY

PCT

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PN0324-PCT	FOR FURTHER ACTION See Form PCT/IPEA/416	
International application No. PCT/NO2004/000199	International filing date *(day/month/year)* 01.07.2004	Priority date *(day/month/year)* 03.07.2003
International Patent Classification (IPC) or national classification and IPC C07C231/08		
Applicant AMERSHAM HEALTH AS et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.04.2005	29.06.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Telephone No. +49 89 2399- 8324 S. Granucheau

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NO2004/000199

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-9 as originally filed

   Claims, Numbers

   1-17 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-17
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-17
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

SECTION V

D1= WO-A-98/08804

1. The present application relates to a process for producing 5-[N-(2,3-dihydroxypropyl)-acetamido]-N,N´-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide (iohexol).

2. Document D1 cited in the description on page 1, line 35 is considered to represent the closest sate of the art. It discloses a process for producing iohexol by reacting 5-(acetamido)-N,N´-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide (5-Acetamide) with a 2,3-dihydroxypropylating agent in the presence of a solvent comprising 2-methoxyethanol and, optionally, isopropanol (see D1, claim 1). The problem to be solved by the present application with respect to the cited prior art is to provide another process for the manufacture of iohexol.

3. The process according to present claim 1 differs from the process of D1 by using a solvent comprising a C_1-C_5-monoalkylether of a C_3-C_{10}-alkylene-glycol. There is no suggestion in the prior art which would have motivated the skilled person to use the above specific solvent in the production of iohexol from 5-Acetamide. Compared to the method according to D1 (cf. D1, Example 1), the amount of iohexol present in the reaction mixture obtained by the claimed process is slightly higher (cf. Examples 1 and 2). Moreover, when the solvent is employed not only in the N-alkylation step but also in the subsequent purification step, the content of the undesired O-alkylated by-products in the final product is significantly lower (cf. Example 2) than in the purified iohexol obtained in D1 (cf. D1, Example 2). This represents an important advantage of the present process regading the use of iohexol as a non-ionic iodinated X-ray contrast agent in medicine (cf. description, page 2, lines 10-15, page 6, line 22 - page 7, line 3).

   Accordingly, the subject-matter of claim 1 meets the requirements of Article 33(2) and (3) PCT.

4. Dependent claims 2-17 concern particular embodiment of claim 1. They fulfil the requirements of Art. 33(2) and (3) PCT as well.

5. The expression "about" in connection with ranges (cf. page 3, line 32) renders the

scope of the application unclear (Art. 6 PCT).

6. The statement "which is hereby incorporated by reference" (cf. page 1, lines 27-28) contradicts the requirements of Rules 5.1(a)(iii) and 9.1(iv) PCT.